46. (Twice Amended) The method as set forth in claim 43, wherein said isolated glycerolipid is extracted from tea, mushrooms, algae or cereal residues.

47. (Twice Amended) The method as set forth in claim 40, wherein said isolated glycerolipid consists of fatty acid and glycerol.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 40-47 have been amended to more particularly define the present invention. Support for the claim amendments is readily apparent from the teachings of the specification and the original claims. Specifically, Applicants have limited the scope of the pending claims to "*isolated*" glycerolipids.

With regard to the objection of the disclosure, Applicants believe that amendment to the specification should be sufficient to overcome this objection. Specifically, the term "900 ml" on page 28, line 15, of the specification has been changed to "900 liters" as per the Examiner's suggestion. Applicants wish to thank the Examiner for recognizing this obvious typographical error.

With regard to the rejection of claims 40-42 and 46 under 35 USC § 102(b) as being anticipated by the old practice of drinking tea, and eating mushrooms or cereals, this rejection has been overcome by the amendments to the claims. To constitute anticipation of the claimed

invention, a single prior art reference must disclose each and every material element of the claim. Here, in this case, the old practices of drinking tea, and eating mushrooms or cereals do not anticipate the administration of an "*isolated*" glycerolipid since such glycerolipids are not isolated in such old practices. Thus, in view of the amendments to the claims, this rejection can no longer be sustained and should be withdrawn.

With regard to the rejection of claims 40-47 under 35 USC § 103(a) as set forth in item 5 of the Official Action, this rejection is deemed to be untenable and is thus respectfully traversed.

To establish a *prima facie* case of obviousness under U.S. practice, the cited references in combination must teach or suggest the invention as a whole and include all the limitations of the claims. Here, in this case, none of the cited references teach a method of inducing apoptosis as defined by the pending claims.

The teachings of each of the cited references are as follows:

1. Hibino et al. teaches that a glycerolipid (diacylglycerol containing DHA) is useful for treating cancer.

2. Gilchrest et al. teaches that natural glycerolipids (diacylglycerol) are known to be similarly active as physiological activator of PKC.

3. Giaccia et al. suggests that PKC activators are useful in treating cancers.

4. Nakai et al. teaches that apoptosis is involved in cancer treatment when the cancer cells are killed.

5. Nelson et al. teaches that acid treatment of materials containing glycerolipid is a well-known technique for glycerolipid separation and purification.

It is clear from the teachings of the cited references that one skilled in the art cannot reasonably predict that apoptosis can be induced by isolated glycerolipid.

Hibino et al. discloses that diacylglycerol with docosahexaenic acid at Sn-2 position shows a differentiation-inducing activity on cancerous cells. Thus, the anticancer mechanism disclosed in Hibino et al. is different from the mechanism of apoptosis taught in the present invention.

Gilchrest et al. discloses that glycerolipid (diacylglycerol) activates protein kinase C to induce melanin synthesis in melanocytes, which has no relationship to the "apoptosis inducing" methods of the present invention.

Giaccia et al. discloses a method of treating a solid tumor which comprises administering to a subject, a compound effective to activate protein kinase C in the cells of the tumor. However, this effect is selective to hypoxic cells. Further, it is disclosed that the mechanism of cell death by hypoxia appears to be necrosis rather than apoptosis (see column 12, line 65 to column 13, line 10, of Giaccia et al.). It is clearly explained on page 1 of the present specification and in Giaccia et al. (see column 1, line 36 to column 13, line 10) that apoptosis is different from necrosis.

Thus, since the cited references neither teach nor suggest apoptosis selective to cancer cells as in the present invention, the present invention is not obvious under 35 USC § 103(a) based on the combined teachings of Hibino et al. (JP01160988), Gilchrest et al. (USP 5,353,440), Giaccia et al. (USP 5,646,185), Nakai et al. (USP Patent 5,672,603) and Nelson ("Isolation and

Purification of lipids from Biological Matrices", in Analysis of Fats and Oil and lipoproteins, edited by Edward G. Perkins, 1993)

The Examiner has also argued in the Official Action that mere recitations of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. The Examiner believes that the cited references in combination teach or at least suggest a method for treating cancer by administering glycerolipid. In other words, from the teachings of these references, the Examiner believes that the present invention is obvious since the prior art methods would **inherently** possess the presently claimed method steps of inducing apoptosis. However, Applicants strongly believe that the Examiner is misapplying the principle of inherency under U.S. practice.

It is clear from § 2112.02 of the MPEP that the Patent Office has taken a position that a new use for an old product ***or old process*** could in fact be claimed as a method. This position is well supported under U.S. statutory and case law. In 35 U.S.C. § 100(b) a "process" is defined as a "process, art or method, and includes a ***new use*** of a ***known process***, machine, manufacture, composition of matter, or material." (Emphasis added.) Further, in *Ex parte Wagner*, 88 U.S.P.Q. 217 (Pat. Off. Bd. App. 1950), the Board of Appeals stated that

> "[M]any processes which are old in a ***procedural sense*** become ***new*** when, by the use of a different (but known) agent, a ***new result*** is accomplished. In considering the patentability of such processes, it appears that ***the real criterion is not whether the steps themselves are shown in the prior art*** but whether the use of the material in the process claimed is suggested by the prior art. It is not

considered proper to disregard the specific nature of the material employed in the claimed process which is responsible for the unobvious result and determine patentability of the process solely on the novelty of the physical manipulative steps recited. If the result of the process is unobvious and the particular use of the material is not suggested by the prior art, the process claims should be allowed." (Emphasis and clarification added.)

As noted above, it has not been known at all, before the filing of the present application, that apoptosis is induced in cells by isolated glycerolipids. The prior art methods of Hibino et al., Gilchrest et al. and Giaccia et al. are based on anti-cancer action of glycerolipids ***using a different mechanism***. Also, it has been known that various mechanisms may be involved in anti-cancer action.

Thus, since the cited references teach a ***completely different use*** (method of treating cancers) for glycerolipid ***under a different mechanism***, it cannot be concluded that the presently claimed method of inducing apoptosis (which is a new use and which produces a new result) is inherently taught by the cited references, especially since the apoptosis inducing action (previously unknown characteristic) of glycerolipid is not expressly disclosed or suggested anywhere in the cited references.

In addition, the Patent Office must also satisfy two additional requirements to establish a *prima facie* case of obviousness. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, *must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine*

references. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vintage point of the skilled artisan at the time the invention was made.

It is clear from the Examiner's comments or lack thereof (regarding motivation) that there is no suggestion or incentive in any of the cited references that would have motivated the skilled artisan to modify or combine the cited references. As it is well known under U.S. practice, motivation is lacking when the state of the art at the time of the invention pointed researchers in a different direction than the inventor proceeded.

The Examiner has reasoned that since Nakai et al. teach that apoptosis is involved in cancer treatment when the cancer cells are killed and that apoptosis regulating compounds or composition are useful as anticancer agents, it would have been obvious to one skilled in the art to use anticancer agents containing glycerolipid (as taught in, for example, Hibino et al., Gilchrest et al. and Giaccia et al.) for inducing apoptosis. Thus, the Examiner has based his obviousness rejection on the relationship that glycerolipid has an anticancer effect (Hibino et al., Gilchrest et al. and Giaccia et al.) and that apoptosis is a mechanism for killing cancer.

However, both of the cited references, Gilchrest et al. and Giaccia et al., teach away from using glycerolipid in a method for inducing apoptosis since, as stated earlier, both references teach a mechanism ("*activating protein kinase C in the cells of the tumor*") unrelated to the apoptosis inducing action of glycerolipid. It should be noted that by teaching away from the present invention, the cited references, Gilchrest et al. and Giaccia et al., sever the logical relationship which form the basis of this obviousness rejection. Further, in view of the fact that

various mechanisms may be involved in anti-cancer action, the fact that glycerolipid has an anticancer effect (as taught in Hibino et al.) cannot motivate one skilled in the art to use glycerolipid in a method for inducing apoptosis especially since Gilchrest et al. and Giaccia et al. teach a different mechanism of glycerolipid in treating cancer.

Further, the proposed combination of the cited references did not have a reasonable expectation of success since from the vintage point of the skilled artisan, it could not have been predicted from the teachings of the cited references that glycerolipid can be use in a new method of inducing apoptosis since such a property is not disclosed in any of the cited references.

Even if it has been known that apoptosis inducing agents are useful as anticancer agents, it cannot be assumed that anticancer agents are useful at inducing apoptosis. As stated above, various mechanisms may be involved in anti-cancer action. Thus, a person of ordinary skill in the art can not predict and thus reasonably expect that an anticancer agent such as glycerolipid is also useful in a new method of inducing apoptosis.

It should be noted that the remaining reference, Nelson, merely teaches the use of acid treatment in lipid separation and purification, and therefore, does not cure or address the deficiencies in the teachings of the cited references and the arguments noted above.

Thus, in view of the reasons outlined above, it is clear that claims 40-47 are unobvious over the combined teachings of Hibino et al., Gilchrest et al., Giaccia et al., Nakai et al., and Nelson and thus, should be withdrawn

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

In view of the foregoing amendments and remarks, it is respectfully submitted that the Application is now in condition for allowance. Such action is thus respectfully solicited.

If, however, the Examiner has any suggestions for expediting allowance of the application or believes that direct communication with Applicants' attorney will advance the prosecution of this case, the Examiner is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

Takeshi SAKAI et al.

By: _____

Lee Cheng
Registration No. 40,949
Attorney for Applicants

LC/gtg
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
December 26, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The claims have been amended as follows:

40. (Four Times Amended) A method of inducing apoptosis comprising administrating an apoptosis inducing agent which comprises isolated glycerolipid as the effective component, to an individual.

41. (Twice Amended) The method as set forth in claim 40, wherein said isolated glycerolipid is derived from plants, microorganisms or animals.

42. (Twice Amended) The method as set forth in claim 41, wherein said isolated glycerolipid is derived from tea, mushrooms, algae or cereal residues.

43. (Twice Amended) The method as set forth in claim 41, wherein said isolated glycerolipid is extracted from plants, microorganisms or animals with an organic solvent.

44. (Twice Amended) The method as set forth in claim 43, wherein said isolated glycerolipid is treated with an acid or an alkali prior to extraction.

45. (Twice Amended) The method as set forth in claim 43, wherein said isolated glycerolipid is purified by hydrophobic, reversed phase, or normal phase chromatography.

46. (Twice Amended) The method as set forth in claim 43, wherein said isolated glycerolipid is extracted from tea, mushrooms, algae or cereal residues.

47. (Twice Amended) The method as set forth in claim 40, wherein said isolated glycerolipid consists of fatty acid and glycerol.

invention having the apoptosis inducing property and anticancer property are/is quite useful as additive(s) to food or beverage.

Examples

The present invention will now be more specifically illustrated by way of the following examples although the present invention is not limited by those examples at all. Incidentally, the term % in the examples means that by weight.

Example 1

Preparation of the Composition Having an Apoptosis Inducing Action from Seaweed

(1) *Gagome kombu* (*Kjellmaniella crassifolia*) was well dried and 20 kg of the dried product was ground by a free grinder (manufactured by Nara Kikai Seisakusho).

Calcium chloride dihydrate (manufactured by Nippon Soda) (7.3 kg) was dissolved in 900 ml liters of tap water and then 20 kg of ground *gagome kombu* were mixed therewith. Temperature of the liquid was raised from 12℃ to 90℃ by bubbling the steam thereinto for 40 minutes and the mixture was kept at 90-95℃ for one hour with stirring and cooled to give 1,100 liters of cooled product.

Then the cooled solution was subjected to a solid-liquid separation using a solid-liquid separator (type CNA; manufactured by Westfalier Separator) to prepare about 900